UKPDS: a Message of Hope and a Need for Change

The results of the huge United Kingdom Prospective Diabetes Study, which recruited 5102 patients and lasted more than 20 years, have clearly demonstrated the magnitude of the risks of hypertension and hyperglycaemia in Type 2 diabetes mellitus and the beneficial effects of achieving optimal control of both.[1–6]

The exposition of the harmful effects of high blood pressure and blood glucose was impressive. Risks of both macrovascular and microvascular damage increased substantially for every 10 mmHg increase of systolic blood pressure and for every 1 % increase of HbA_{1c}. The increases were documented for any diabetes-related end-point (macrovascular and microvascular disease together), diabetes-related deaths, myocardial infarction, stroke and microvascular complications (retinopathy and albuminuria). The risks were additive and reached alarming levels when both these prime factors were elevated. There was no threshold level of risk for either blood pressure or blood glucose.

The considerable benefits of 'tight control' aiming for a blood pressure of less than 150/85 and fasting plasma glucose of less than 6 mmol l^{-1} are at last clear cut. The risks for most (but not all) of the end-points listed above are reduced, sometimes substantially. It is to be expected that macrovascular end-points benefit most by blood pressure control and the achievement of a mean blood pressure of 144/82 (systolic pressure 10 mmHg below that of the less intensively treated group) resulted in reduction in risk of diabetes-related deaths (32 %), stroke (44 %) and indeed all diabetes-related end-points. Risk of myocardial infarction was reduced (but not quite significantly) by tight blood glucose control but not by blood pressure control.

The decrease in the risk of microvascular end points, especially the need for photocoagulation, by improved diabetes control is impressive enough (25 %) but the importance in this regard of blood pressure control is important for clinicians to know—the risk of microvascular end-points is reduced by 37 % (again, predominantly due to reduction in need for photocoagulation), with an accompanying reduced risk of 47 % of vision declining by three lines, as a result of protection from macular disease. The evolution of microalbuminuria is also influenced by glycaemic control (reduced risk after 9 years), while neuropathy seems, as in other studies, to be most resistant. It is only after 15 years that any beneficial effect on biosthesiometer measurements (but not heart rate variation) may be observed.

The inexorable deterioration of the diabetic state which occurs over a decade regardless of treatment mode must concern all doctors and make them aware of the serious challenges which they and their patients face in trying to achieve 'tight control'. Yet despite the obvious progression of the disease, a clear difference of HbA_{1c} of 0.9 % was maintained throughout the UKPDS (the mean HbA_{1c} in the 'tight control' group was 7.0 % compared with 7.9 % in the conventionally treated group). It is of course this insidious decline and the slow rate of progression of complications that makes the study of their evolution and the benefits of treatment so complex: significant benefits of blood glucose control need almost a decade, although effectiveness of blood pressure control is observed sooner. The implications of these observations must be considered when determining the appropriateness of 'tight control'.

Answers to questions regarding added efficacy of different forms of treatment for diabetes have at last been answered by UKPDS. The importance of tight blood glucose control is clearly the key and all means of achieving it have the same effect. The use of insulin *per se* confers neither additional advantages nor disadvantages, while the use of sulphonylureas does not lead to additional risks. (Chlorpropamide did perform worse, as its use was associated with a rise in blood pressure over the years). Metformin used alone for overweight patients is very effective, more so apparently than when used in combination with sulphonylureas, where some conflicting evidence raises new questions but does not indicate any need to change its present use where glycaemic control is optimal. The role of diet, exercise and weight reduction remain, of course, paramount in treatment of Type 2 diabetes. It is helpful for physicians to know that ACE inhibitors or β blockers are equally effective in achieving the benefits of lowering blood pressure which are so clearly described in this group of patients.

Intensive treatment is no simple matter. It requires dedication on the part of the physician and the will to comply on the part of the patient. Polypharmacy may be needed to implement tight control and it is estimated that one new treatment will need to be added every 4 or 5 years. Yet the study shows no overall deterioration in quality of life as a result of intensified treatment. On the other hand, increased anxiety when eye complications develop is entirely understandable and a clear measure of the life-long tension experienced by people with diabetes, for whom the benefits of this study are so important. Of course, hazards of severe hypoglycaemia always exist whenever insulin is needed, affecting about 1.8 % of those taking it. Intensive treatment led to a significant weight gain (mean 2.9 kg), which was greatest for those taking insulin (4.0 kg).

How should we proceed in tomorrow's clinic? First, the primary aim must continue to be to ensure the relief of symptoms and best possible quality of life for our

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individual patients. Selection of people to whom tight control policies should be aimed depends on factors which may be difficult to define but must at least include a potential predicted lifespan which will allow real benefits. Second, patients need to be enthusiastic to comply with treatment and undertake lifestyle changes which are not always easy. Physicians should be aware that tight blood pressure control overall has larger benefits which are manifest sooner than those of blood glucose control. We must be careful to avoid doing more harm than good by inducing anxiety when treatments fail, as they often do, and we will need to monitor the potential problems of polypharmacy—almost inevitable in some patients—and avoid inappropriate advice. People need to know what is harmful and the clear benefits of good treatment. Research needs to seek and implement new and better techniques. Those who cannot cope with the rigors of tight control also need to know that their care still comprises many other facets, not least the continuing importance and benefits of complications screening leading to early diagnosis and effective interventions.

Implementation of the findings of the UKPDS will need a programme of education for all health professionals, people with diabetes and the public. The messages must be taken up by government and health authorities, because they have important implications for service provision. With new targets to achieve, there is an even greater need than before for close collaboration between primary and secondary care. And it need not break the bank—the cost-effectiveness of intensified treatment for Type 2 diabetes compares very favourably with initiatives such as the implementation of the 4S cholesterol lowering study, population screening for cardiovascular risk, breast cancer screening and cardiovascular lifestyle advice, and other established health care programmes, at least in the UK.

What are the messages? The most important is that the aims of treatment for Type 2 diabetes should be set near normality, at least for patients diagnosed between the ages of 25 and 65. Can we do it? One way towards the new goals might be to use the UKPDS study protocols as guides in clinical practice. We have evidence that they work! Involvement of patients is crucial. They must be informed of the natural progression of the disease and so not regard intensification of therapy over time as worsening of the disease, and physicians must remember that the need for increasing therapy may not be due to poor compliance. Insulin should not be considered as a punishment for treatment failure or a last resort for the severely ill. And the overwhelming message is that complications are not inevitable and can be actively avoided. Patients themselves can monitor their need for further therapy when fasting plasma glucose is over 6 mmol l^{-1} or blood pressure is over 145/85.

UKPDS is a landmark in the history of diabetes. The Oxford team and all their collaborators must be congratulated on their vision, perseverance and huge achievements over more than 20 years. Now it is up to us to use the results of their labour.

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